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Genetics, Genetic Testing and Biomarkers of Digestive Diseases

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Editor's Introduction

The discipline of gastroenterology, hepatology and pancreatology has changed dramatically since its inception as a specialty of internal medicine. The specialty originally focused and pursued an understanding of the pathology and physiology of the gastrointestinal tract, liver and pancreas scientifically, something which is still in active evolution.. We began to comprehend gut motility, stomach acid secretion, the epidemiology of digestive cancers, autoimmune diseases of the gut, pancreas and liver, and how infectious diseases are transmitted and affect the GI tract. Treatment slowly became possible with the acquired knowledge, and created approaches for therapeutics. Histamine type 2 blockers and proton pump inhibitors, nucleotide and nucleoside analogs, immune modulators, and a myriad of antibiotics have been studied and used effectively to alleviate patient suffering from GI diseases. Radiological imaging helped determine the absence, presence, or extent of disease non-invasively. Endoscopy of the alimentary tract and its related growing list of special devices have provided a huge leap forward in caring for patients with GI disease, allowing direct visualization of and sampling from the GI tract, and providing an avenue for direct therapeutic intervention.

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We have now entered the genomic era, providing another leap forward in the care of patients with GI diseases. This era commenced with the identification genetic mutations as the basis of Mendelian-inherited diseases involving the GI tract, such as familial adenomatous polyposis [1,2], cystic fibrosis [3–5], and genetic hemochromatosis [6]. The genetic information could be predictive if one carried the mutation; it could be also be predictive to family members when they did not carry the mutation, foregoing unnecessary surveillance efforts and applying those healthcare resources aptly to mutant carriers. Genetic information has progressed dramatically and now extends past heritable diseases; it applies to many GI conditions in terms of risk (e.g. genome wide association studies or GWAS, or the presence or absence of a mutation directly within tumor tissue), prediction of biological behavior, outcome and survival, and in the approach and use of therapeutics (e.g. cetuximab in wild type *KRAS* colorectal cancer, or 6-thioguanine and 6-methylmercaptopurine metabolite levels for optimal use of azathioprine or 6-mercaptopurine). The field is rapidly evolving. A convergence of advancing knowledge of GI tract disease, technical advances and reduced costs for next generation sequencing and other analytic technologies such as proteomics and metabolomics, easier access to sampling human tissue with advances in image-directed biopsies and minimally invasive tissue removal, and a growing number of interventions discovered to improve the health of patients with GI diseases make this era an exciting time for helping our patients and fundamentally changing our GI practices.

Biomarkers are a key part of precision (personalized or individualized) medicine. Molecular biomarkers are derived from the genetic, genomic and other high-throughput platforms in analysis of blood, tissue, fecal, urine or other biological material that can inform the practitioner on the next best course of action for the individual patient [7]. Biomarkers ideally lead to prescriptive targeted treatment changes that can improve the outcome of patients with GI disease; this is the essence and part of the definition of precision medicine [8]. Biomarkers can also be diagnostic or prognostic, being more informative for a clinical course rather than a targeted individualized treatment prescription. The assumption and reality is that GI patients with a specific disease are biologically heterogeneous, and molecular biomarkers can differentiate patients into subtype groupings of more homogeneous individuals sharing an actionable characteristic amenable to molecularly targeted therapies beneficial to that subgroup or individual. Both biomarkers and targeted individualized therapies are the cornerstone of President Obama’s Precision Medicine Initiative put forth in early 2015 [9]. This initiative aims to further revolutionize the practice of medicine by generating additional scientific evidence to move the concept of precision medicine into everyday clinical practice. Parallel and complimentary ventures such as the 100,000 Genomes Project in the UK aim to identify novel genetic diagnoses and create opportunities for the use of genomics in healthcare [10].

This special issue of *Gastroenterology* lays a foundation and provides a current understanding to the approach to precision medicine for several GI disorders, a timely topic given the growing international investments in personalized care. We as editors of this special issue, along with the entire *Gastroenterology* Board of Editors, selected the topic of genetics, genetic testing, and biomarkers in digestive diseases because of the rapid advances in these topics among the GI diseases over just the past few years. Recent studies outlined in

many of the articles within this special issue highlight how fast information has moved, and how quick biomarkers and potential therapeutic targets for treatment purposes are lining up for phased human clinical studies, pharmaceutical testing portfolios, and routine patient use. The transformation from bench to practice has been greatly accelerated with newer and cheaper genomic analytic capabilities and information technologies, and rapid dissemination of information. New molecular biomarker tests are being put out to the clinical commercial market on a regular basis. Many aspects of this rapid change have and will continue to become part of daily clinical GI practice.

For this special issue of *Gastroenterology*, we recruited leading authorities to update our readers in the genetics, genetic testing, and biomarkers of digestive diseases. The 12 reviews and 2 commentaries in this issue cover many aspects of the GI tract, hepatobiliary system and pancreas. The two commentaries are more general than disease-focused, and deal with the generation and recording of genetic information. The commentary by Ananthakrishnan and Lieberman examines the current and future ideal use of electronic health records for genetic and biomarker information that pertains to the practitioner and researcher, laboratory, and patient [11]. Ngeow and Eng's commentary addresses a path forward in the post-genomic area, including the examination of gene-gene or gene-environment interactions, and clinical implementation of genomics [12]. Among the 12 disease-focused reviews, four articles examine biomarkers and genetics and their clinical application in colorectal cancer (CRC). Stoffel and Boland provide genetic testing insights in inherited forms of CRC [13], and Carethers and Jung highlight the genetics and potential biomarkers for use in patients with sporadic CRC [14]. Okugawa, Grady and Goel showcase how epigenetic alterations in CRC provide biomarkers for patient care [15], and Robertson and Imperiale review the clinical application of biomarkers within stool tests for CRC screening [16]. Three articles focus on the rapidly advancing use of genetics and biomarkers for inflammatory bowel disease (IBD). McGovern, Kugathasan and Cho provide an update on GWAS data from large IBD studies [17], Dubinsky and Braun showcase the use of microbial biomarkers for IBD diagnosis [18], and Sands highlights inflammatory biomarkers for IBD [19]. Two articles focus on the liver: Pietrangelo reviews classic hemochromatosis genetics and testing [20], and Zucman-Rossi, Villaneuva, Nault and Llovet provide a comprehensive review of the genetics and biomarkers for hepatocellular carcinoma [21]. The remaining three reviews highlight the esophagus, stomach, and pancreas. Reid, Paulson and Li present the most up-to-date genetic analyses of Barrett's esophagus and esophageal adenocarcinoma [22]. Tan and Yeoh supply the latest insights of the genetics of gastric adenocarcinoma [23], while Whitcomb, Shelton and Brand present the latest on the biomarkers and genetics of inherited and sporadic forms of pancreatic cancer [24]. We are very grateful to the contributing authors as well as the insightful manuscript reviewers and editorial staff for their time and energy in creating these outstanding articles with useful figures and tables for the readers of *Gastroenterology*.

We hope that readers of this special issue of *Gastroenterology* will find it full of new insights into this rapidly moving field in clinical GI practice. We hope you enjoy the up-to-date information, and see the alignment with current and future aspects of the Precision Medicine Initiative and the other related global efforts. We trust that this issue provides a

new and timely reference as precision medicine, biomarkers, and genetics move more fully into GI clinics to direct patient care.

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Abbreviations used

GI gastrointestinal

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